

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ORYZALIN

Chemical Code # 001868, Tolerance # 00304
SB 950 # 223

April 24, 1987
Revised 6/16/88, 11/22/89, 5/28/93

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect.
Oncogenicity, rat:	No data gap, possible adverse effects.
Oncogenicity, mouse:	No data gap, no adverse effect.
Reproduction, rat:	No data gap, no adverse effect.
Teratology, rat:	No data gap, no adverse effect.
Teratology, rabbit:	No data gap, no adverse effect.

Gene mutation:	No data gap, no adverse effect.
Chromosome effects:	No data gap, no adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	Not required at this time.

Toxicology one-liners are attached.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T930528

Current revision by Aldous, 5/28/93

All relevant record numbers through volume 304-090 (Record No. 119900) listed by the DPR Library printout as of 4/30/93 have been included in this Toxicology Summary. All relevant records of the 900,000+ series are included.

Note: these pages contain summaries only. Individual worksheets may identify additional effects.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

CHRONIC TOXICITY, RAT

304-020 995139 "The Toxicological Evaluation of Oryzalin (EL-119) Given to Rats in the Diet for One Year", (12/1978, Lilly Research, Study R-157). Fischer 344 rats; Oryzalin, 96.5%, lot X-28607; dose levels of 0, 300, 900 and 2700 ppm in diet; 15/sex/group. Slight decrease in body weight gain in the high-dose females of approximately 10-11%, but no effect in males; slight hematological and biochemical differences and increased organ weight (liver, kidney). NOEL = 900 ppm (decreased weight gain in females, increased organ weights). **UNACCEPTABLE** (one-year study), incomplete. (Appendices A and B not included, no urinalysis). This is an interim sacrifice for the two-year study, Record numbers 995135 and 38445, below under ONCOGENICITY, RAT. Apostolou, 6/13/85, and Gee, 4/3/87

NOTE: The reproduction study (087:116321) did not establish a NOEL for systemic effects down to the lowest dose tested (250 ppm). Thus the latter LEL would be the relevant value for rat chronic effects evaluation. Aldous, 5/28/93.

CHRONIC TOXICITY, DOG

052, 053 50461, 50462 "A One-Year Chronic Oral Toxicity Study of Oryzalin (Compound 67019, EL-119) in Beagle Dogs", (11/12/86, Hazleton, Study 6180-102 (HLA) and D00385 (Lilly)). Oryzalin, 98.9%; given in gelatin capsules at 0, 1.5, 5, 15/250/500 or 50 mg/kg/day; 15 mg/kg increased to 250 at week 15 and from 250 to 500 mg/kg at week 33; 4/sex/group; dose selection based on subchronic studies in which 56.25 mg/kg caused "severe anemia" in 2/4 males in a three-month study. (In the present study, 500 mg/kg/day elicited mild, but consistent reductions of RBC/Hb/HCT parameters in females: a comparatively weak response). NOEL = 5 mg/kg/day (increased liver weight, clinical chemistry values with increased cholesterol and serum alkaline phosphatase); no adverse effect reported; **ACCEPTABLE. Gee, 4/2/87

ONCOGENICITY, RAT

****025 995135, 026 038445** "The Toxicological Evaluation of Oryzalin (Compound 67019) given to Fischer 344 Rats in the Diet for Two Years", (3/1980, Lilly Research, Studies R-167 and R-177). Rat-Fischer 344; Oryzalin, two lots - 96.5 and 96.0%; dose levels of 0, 300, 900 and 2700 ppm in the diet; 60/sex/group. NOEL = 300 ppm; decreased hematologic parameters. A **"possible adverse effect"** was indicated by benign skin, mammary and thyroid follicular cell tumors. **ACCEPTABLE** as an oncogenicity study, not as a chronic toxicity study, due to inadequate sampling intervals for hematology, clinical chemistry, urinalysis and no eye exam. Apostolou, 6/17/85 and Schreider, 8/6/86.

EPA one-liner #1: NOEL = 300 ppm (LDT); LEL = 900 ppm (decreased RBC, Hct, Hb; increased leukocyte counts, increased liver and kidney wts, inhibition of growth, decreased survival, oncogenic potential still undetermined however, an increase in skin tumors is seen in both sexes. The increase in thyroid tumors was found not to be significant.) Core grade: minimum.

EPA one-liner #2: *Risk assessment. Skin tumors - "Basal cell and related adenomas or tricepitheliomas" $Q_1 = 3.4 \times 10^{-2}$. Core grade: Minimum.

[A response by the registrant to the CDFA reviews notes that in the toxicology finding and risk assessment of EPA in the Federal Register, Volume 49, No. 226, pages 45854 and 45855, there is an error in conversion of the ppm in the diet to mg/kg/day.]

040 042725 (1980, Lilly Research; 1981, Lilly-Neoplasm incidence tables) Addendum to #995135, 026 38445 - 8 additional tables

044 042864 Addendum to #995135. Historical incidence of thyroid follicular hyperplasia in control Fischer 344 rats from 24 oncogenic studies started from 1976 - 1983.

****** Discussion of chronic data: In the preparation of the Toxicology Summary, certain of the studies were reexamined and the total data in all of the studies, including the three-month and one-year rat studies, were considered. The primary deficiencies in the rat study preventing it from being guideline for a combined/chronic study were the omission of the urinalysis and eye exams, and several currently required parameters in clinical chemistry

(cholesterol, serum electrolytes) were not quantitated. Diet analyses were conducted. Considering that there is an acceptable chronic dog feeding study and an acceptable mouse oncogenicity study, with no evidence in histopathology of any study for kidney or liver effects, the weight of evidence of the collective data is considered adequate for evaluation of long-term feeding effects in animals. No further chronic feeding study is required at this time. Gee, 4/24/87.

ONCOGENICITY, MOUSE

304-022 995134, 304-023 038443, 304-024 038444 "The Toxicological Evaluation of Oryzalin (Compound 67019) given to B6C3F₁ Mice in the Diet for Two Years", (3/1981, Lilly Research, Studies M-9087 and M-9097). B6C3F₁; Oryzalin, 96.5%, lot x-28607; dose levels tested 0, 500, 1350 and 3650 ppm in the diet; 60/sex in control group and 40/sex in each treatment group with two studies run in parallel at same the doses and numbers of animals. Slight increase in liver weights with no histopathology finding, no tumor effect. Systemic NOEL = 1350 ppm (decreased weight gain in females), onco NOEL \geq 2700 ppm (nominal); **ACCEPTABLE. This study was initially reviewed by Apostolou as a combined study for which some required data were missing and therefore was unacceptable. The review also noted a possible adverse chronic effect with an increase in liver organ weight but no oncogenic effect. The liver effect was not substantiated by histopathological exam and therefore is not considered of biological significance. With the change in category to oncogenicity, the study becomes acceptable. Apostolou, 6/13/85 and Gee, 4/22/87.

EPA one-liner: Oncogenic NOEL > 3,650 ppm (HDT); systemic NOEL = 500 ppm; systemic LEL = 1,350 ppm, significant ($p < 0.05$) (decreased wt. of uterus plus ovary, which is dose-related, in female mice) Core grade: Minimum.

[The decreased uterine weight stated to be due to lower incidence of cystic endometrial hyperplasia in oryzalin groups.]

304-039 042724 Single volume duplicate of vols. 022 to 024, above.

304-020 995133 "The Toxicological Evaluation of Oryzalin (Compound 67019) given to Mice in the Diet for One Year", (6/1979, Lilly Research, Study M-9137). B6C3F1; Oryzalin, 99.8%; dose levels tested were 0, 500, 1350 and 3650 ppm in diet; 15/sex/group; very slight hematological and serum chemistry changes, slight increase in kidney relative weight to heart and testes, cystitis in high dose females. **UNACCEPTABLE** (study of too short duration, too few animals, etc.); incomplete (Appendices A and B not included, no urinalysis performed). This is the one-year interim sacrifice segment for the report in Records 995134, 38443 and 38444 (above). Apostolou, 6/13/85. No EPA one-liner.

REPRODUCTION, RAT

** NOTE: **The reproduction study data gap is filled** by the older multigeneration study (304-021:995145), supplemented by an ancillary study (304-087:116321). No adverse effects were indicated. No individual study is independently acceptable, however the ancillary study was conducted specifically to address the deficiencies in the older study. Aldous, 5/11/93.

304-021 995145 "A Multigeneration Study with Compound 67019 in the Rat", (Lilly Research, Studies R-1226, R-327, and R-647; 1/21/80). Oryzalin technical, 99%, was administered in feed to groups of 25 Fischer 344 rats/sex at dose levels of 0, 0.025, 0.075 and 0.225% (i.e. 0, 250, 750, or 2250 ppm). There was a slightly decreased weight gain at the high dose. Reproductive NOEL = 0.225%. Developmental NOEL = 750 ppm, based on decreased weight gain during lactation. Previously reviewed as unacceptable due to lack of necropsies on scheduled sacrifices, an absence of gross exams on reproductive organs, and lack of histopathology on reproductive tissues from high dose and control animals (Apostolou, 6/12/85 and Schreider, 7/29/86). After review of the supplemental information presented in record #076010, the study remained **UNACCEPTABLE**, and was determined to be not upgradeable, because it was clear that no information was available to substitute for lack of histopathology on F0 and F1 adults in a reproduction study (Chernoff, 11/6/89). [The data gap was subsequently filled after submission of an ancillary study (Record No. 116321, below).]

EPA one-liner: Reproduction NOEL > 2250 ppm (highest level tested), fetotoxic NOEL = 250 ppm (LDT); fetotoxic LEL = 750 ppm (depressed growth). Core grade: Minimum.

304-074 076010 Supplemental information to record no. 995145.

304-087 116321 Hoyt, J.A., Beckhelm, G.A., and Jordan, W.H., "A One-Generation Reproduction Study in Fischer 344 Rats Maintained on Diets Containing Oryzalin (EL-119, Compound 067019)". Toxicology Research Laboratories, Lilly Research Laboratories, Greenfield, IN., June 25, 1992. This is a supplementary study performed to address unreconciled deficiencies in the primary reproduction study: 304-021 995145. The F0 generation included 40 rats/sex/group at 0, 250, 750, or 2250 ppm in diet (mean intake during the premating phase for low to high dose groups respectively was 19, 59, and 179 mg/kg/day for males and 22, 68, and 206 mg/kg/day for females). Mean food intake during growth of F1 rats was about 5% less than above. The most important design feature of this study was histopathology of reproductive organs and of anticipated target organs on all F0 and F1 young adult rats. Commonly evaluated reproductive parameters were measured for F0 \times F1 litters. No systemic parental NOEL was found: findings extending down to the lowest dose level included elevated kidney weights (F0 and F1 males), elevated liver weights (F1 males), and cortical tubular hyaline droplets in kidneys of both sexes of both generations. Other important findings included "minimal" degree of cortical tubular nephrosis in 750-2250 ppm F0 and F1 females (no comparable changes in males), and hypospermatogenesis in 2250 ppm F1 males (typically of "slight" degree). Mean pup weights at weaning of 2250 ppm F1 pups were reduced by 10% (statistically significant). There were modest, but consistent (statistically significant) decrements in adult body weights in F0 and F1 high dose males and females throughout the study. In addition, 750 ppm F1 males trailed slightly, but statistically significantly, behind control body weights during the growth phase. There were no reproductive effects noted other than a small (ca. 10%) decrement in pup weights in 2250 ppm weanlings. This supplementary study suffices to fill the remaining "reproductive study" data gap requirements. **No adverse effects** are indicated by the above findings, however a lack of NOELs for findings in this study suggests that this study be examined if risk assessment is conducted for this material. Kishiyama and Aldous, 5/28/93.

304-090 119900 U.S. EPA worksheet for 304-087 116321, above (noted in DPR worksheet for the same report).

304-042 042731 "A Pilot Reproduction Study on Lilly Compound 67019, Oryzalin, in the Rat, Study R-926", (5/1978, Lilly Research). Pilot reproduction study for #995145. Oryzalin, 99%, given by oral gavage days 6 - 15 of gestation at 0, 25, 75 or 225 mg/kg/day, five females per group. [Pilot seems more appropriate for the rat teratology study, #995142 below.] No clinical effects reported. Schreider, 7/29/86.

042 042734 (1980, Lilly Research) Duplicate of 995145 plus additional pages of eye exam, dated March 2, 1981, Lilly Research - supplemental eye data) Addendum to #995145. See below. Report on eyes states the conditions were considered to be of infectious origin and not treatment-related.

TERATOLOGY, RAT

072 075483 "A Developmental Toxicity Study of Oryzalin (EL-119, Compound 067019) Administered Orally To CD Rats", (Lilly Research Laboratories, Project ID R37988, 6-15-89). Oryzalin, Lot No. L1385A, 96.2%, was administered to groups of 25 CD rats by gavage in 10% aqueous acacia solution at dose levels of 0 (vehicle control), 50, 225 or 1000 mg/kg/day on days 6-17 of gestation. Signs of maternal toxicity (decreased weight gain and alopecia) were observed at 225 and 1000 mg/kg/day. Signs of intrauterine growth retardation appeared in a dose response fashion starting at the lowest dose tested (delayed ossification at all treatment doses; decreased fetal weight at mid and high doses; runts and diaphragmatic hernias at the high dose). Maternal NOEL = 50 mg/kg/day (decreased weight gain and alopecia). Developmental NOEL < 50 mg/kg/day (intrauterine growth retardation). Developmental NOAEL = 50 mg/kg/day. No adverse effects. **ACCEPTABLE. D. Shimer, 10-5-89, G. Chernoff, 11/9/89.

005/021/043 995141 "A Teratology Study with EL-119 in the Rat", (8/72, Lilly Toxicology Labs, Study R-22). Rat, Harlan; Oryzalin - lot 721-98A-042-5, purity not stated; dose levels tested

were 0, 250, 750 and 2250 ppm in diet, 25/group, days 6 - 15. No teratology reported up to 2250 ppm. **UNACCEPTABLE** (no purity of test article, no analysis of diets, no MTD). Apostolou, 6/12/85 and J. Gee, 6/15/88.

EPA one-liner: Maternal NOEL > 2250 ppm (HDT); teratogenic NOEL > 2250 ppm (HDT); fetotoxic NOEL > 2250 ppm. Core grade: None given. NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/2/89) notes EPA classification as "Unacceptable".

304-060 058887 Stability of test article in diet, submitted in support of study 005/021/043 995141, above.

304-021/043 995142 "A Teratology Study on Lilly Compound 67019, Oryzalin, in the Rat", (5/78, Lilly Research, Study R-1186). Rat - Wistar; Oryzalin, 97.4%; dose levels of 0, 25, 75, 225 mg/kg/day by oral gavage, 25 per group, days 6 - 15 of gestation; 12/group sacrificed on day 20, the remainder allowed to deliver pups; no teratology effects up to 225 mg/kg/day; no maternal toxicity up to 225 mg/kg/day. **UNACCEPTABLE** (no evidence of MTD, no analysis of dosing solutions, protocol - resulted in inadequate number of animals examined for fetal effects). Rebuttal in 304-060 explains that this study was conducted to examine heart anomalies in fetuses and in weanlings and was not designed as a standard teratology study. Record # 995141 was the study for satisfying regulatory requirements. The collective data remain unacceptable based on the dose selection and the lack of analyses for actual content of the active ingredient. Apostolou, 6/12/85 and J. Gee, 6/15/88.

EPA one-liner: Fetotoxic NOEL > 225 mg/kg (HDT), teratogenic NOEL > 225 mg/kg (HDT), maternal NOEL > 225mg/kg. Levels tested by gavage in Wistar strain. Core grade: Minimum.

042 042732 "A Pilot Reproduction Study on Lilly Compound 30545 in the Rat", Pilot study to #42740 (below), (8/78, Lilly, Study No R-1066). Compound 30545 is an intermediate material used in manufacturing oryzalin; 5/group Wistar rats; oral gavage at 25, 75 or 225 mg/kg day; days 6-15 gestation; no significant weight loss in treated dams; fetal weights not given; no external effects were observed and no reproductive performance effects were seen. Supplementary data. Schreider, 7/29/86.

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/2/89) notes EPA classification as "Core Supplementary".

304-060 058888 Individual maternal body weight data for 304-021/043 995142, above.

043 042740 "A Teratology Study on Lilly Compound 30545 in the Rat - Study R-1106", (8/78, Lilly Research). Compound 30545 - an intermediate in the manufacture of oryzalin, was tested at 0, 25, 75 or 225 mg/kg by gavage; No adverse effects were identified; NOEL was greater than 225 mg/kg; Initially reviewed as unacceptable and not upgradeable but changed to supplementary data. Schreider, 7/25/86 and J. Gee, 6/15/88.

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/2/89) notes EPA classification as "Core Supplementary".

TERATOLOGY, RABBIT

042 044071 "A Pilot Reproduction Study on Lilly Compound 67019 (Oryzalin) in the Rabbit", (10/78, Lilly, Study B-7326). Oryzalin, technical, 99%; given by oral gavage at 0, 25, 75 or 225 mg/kg to 4/group; NOEL not clear; Study may be supportive of #995143 below.

UNACCEPTABLE, not upgradeable. Study was intended as a pilot study. Schreider, 7/30/86.

EPA one-liner: Maternal NOEL = 75 mg/kg, fetotoxic > 225 mg/kg (HDT). Core grade: not given.

021/043 995143 "A Teratology Study on Lilly Compound 67019 (Oryzalin) in the Rabbit", (9/1978, Lilly Research, Study B-7366). Rabbits, Dutch Belted; Oryzalin, 97.4%; dose levels tested at 0, 25, 55 and 125 mg/kg/day by oral gavage; 15/group, days 6 - 18. Trend in increased resorptions and decreased litter size and body weight but no increase in structural anomalies. Maternal feed consumption and body weight decreased at 55 and 125 mg/kg/day.

UNACCEPTABLE (no analysis of dosing solutions), possibly upgradeable. Apostolou, 6/13/85.

EPA one-liner: Levels tested by gavage in Dutch Belted; fetotoxic NOEL = 25 mg/kg; maternal NOEL = 25 mg/kg; teratogenic NOEL > 125 mg/kg (HDT). Core grade: guideline.

043 042733 "A Pilot Reproduction Study on Compound 30545 in the Rabbit, Pilot study to #42741 (below), (8/78, Lilly Research). Compound 30545 is an intermediate used in making oryzalin; 4 Dutch Belted rabbits/group were given 0, 25, 75, or 225 mg/kg/day oral gavage on gestation days 6-18; two of four pregnant does did not have live fetuses at the high dose; maternal and embryo toxicity occurred, apparently due to the acute toxicity of the test substance. Schreider, 7/29/86.

043 042741 "A Teratology Study on Compound 30545 in the Rabbit - Study B-7526", (3/78, Lilly Research). Compound 30545 - an intermediate in the manufacture of oryzalin (89.8%) given by gavage at 0, 25, 75 or 225 mg/kg; 15 per group; No adverse effects reported; NOEL = 225 mg/kg (HDT); initially reviewed as acceptable but changed to Supplementary data based on being an intermediate and not the active ingredient. Schreider, 7/28/86 and Gee, 6/16/88.

043 042742 "A Replicated Teratology Study on Oryzalin (EL-119, Compound 67019) by the Oral Route in Dutch Belted Rabbits", (1982, Lilly Research, Studies B7281 and B7291). Oryzalin, tech., (96%), given by gavage at 0, 10, 25, 55 or 125 mg/kg; 30 per group; **NO ADVERSE EFFECT reported; NOEL = 125 mg/kg (HDT) for maternal toxic, teratogenic and fetotoxic effects. **ACCEPTABLE.** Schreider, 7/28/86.

EPA one-liner: Teratogenic NOEL > 125 mg/kg (HDT), fetotoxic NOEL > 125 mg/kg (HDT), maternal NOEL > 125 mg/kg (HDT). Core grade: minimum.

GENE MUTATION

041 042726 "The Effect of Oryzalin (Compound 67019) on the Induction of Reverse Mutations in Salmonella typhimurium using the Ames test", (6/83, Lilly Research). Oryzalin technical, lot 95Y47, 96%; strains TA1535, TA1537, TA1538, TA98 and TA100; tested at 0, 25, 50, 100, 200 or 300 ug/plate; with and without rat liver activation, triplicate plates; No mutagenic effects; Initially reviewed as unacceptable based on the single trial but upgraded to **ACCEPTABLE status as a result of the change in guidelines in May, 1987. Schreider, 8/8/86 and Gee, 6/15/88.

EPA one-liner: 25, 50, 100, 200, 300 ug/plate without activation - negative 25, 50, 100, 200, 300 ug/plate with activation - negative. Core grade/document number: Unacceptable/003509; Acceptable/004342.

073 074908 "The Effect of Oryzalin (EL-119, Compound 67019) on the Induction of Reverse Mutations in Salmonella typhimurium and Escherichia coli Using the Ames Test", (Lilly Research Laboratories, Project ID: 880215AMT1188 and 880229AMS1188, 5-20-88). Oryzalin, Lot L-1385A (purity of 96% from another study), was tested in the Ames plate incorporation test with S. typhimurium strains TA1535, TA1537, TA98, TAS100 and E. coli WP2uvrA- (a tryptophan auxotroph) at levels of 0 (DMSO), 6.25, 12.5, 25, 50 or 100 ug/plate, with and without male Aroclor-induced rat liver metabolic activation, triplicate plates, single trial. Concentrations selected were based on a preliminary trial with TA100 and on a precipitation study. No increase in the number of revertants was seen. **No adverse effects. ACCEPTABLE. D. Shimer and Gee, 11/8/89.

045 042870 "The Effect of Lilly Compound 67019, Oryzalin, upon Bacterial Systems Known to Detect Mutagenic Events", (12/4/1979, Lilly). Oryzalin (lot 090-310-146, purity unknown) tested at 0.1 - 1000 ug/ml in Salmonella and E. coli; strains G46, TA1535, TA100, C3076, TA1537, D3052; gradient plate method, single trial; No mutagenic effects. **UNACCEPTABLE**, not upgradeable. Schreider, 8/7/86.

EPA one-liner: Not mutagenic at test levels of from 0.1-1000 mcg/ml in Salmonella typhimurium LT-2 (G46, TA 1535, TA100, C3076, TA1537, C3052, TA1538 and TA 98 and in E. coli WP2, WP2 uvrA-). Core grade: Inadequate.

304-050 050458 Appendix C, mislabeled as SCE data: data contain a mutagen screen using bacterial systems. These data refer to 045:042870, above.

CHROMOSOME EFFECTS

****041 042728** "The Effect of Oryzalin (Compound 67019) on the in vivo Induction of Sister Chromatid Exchange in Bone Marrow of Chinese Hamsters - Studies 810601SCE, 810707SCE, 810720SCE", (12/1981, Lilly Research). Oryzalin, 96%; given either i.p. or orally to female Chinese hamsters at 0, 200, 300, 400 or 500 mg/kg in one dose. At 21 hours (2 hours after colchicine injection), animals were sacrificed and the femurs flushed; 25 cells per animal were analyzed; an increase in SCE's was seen in two trials with i.p. injection; no increase after oral administration. The effect apparently is subject to route of administration. **ACCEPTABLE**. The study was initially reviewed as unacceptable due to no justification of the use of only female with no justification. The registrant responded to this and to the notation of the number of animals with a discussion and submission of a publication from the laboratory, Record #50457, Document 304-050. In view of the positive findings in the females following intraperitoneal injection, the absence of data in males is not considered a major deficiency. If the total numbers of animals in each dose group in the two trials are considered collectively, there are acceptable numbers. The study is upgraded to acceptable. Gee, 8/12/86 and 4/24/87.

EPA one-liner: Positive response by intraperitoneal route, negative orally. Core grade: Adequate.

041 042729 "A Dominant Lethal Study with Oryzalin (Compound 67019) in the Wistar Rat - Study R06082", (10/1982, Lilly Research). Dominant Lethal Oryzalin, technical (96%) given by gavage at 0, 0.5, 2.0 g/kg/day; 15 males/group, dosed five consecutive days, mated 1:1; negative; **UNACCEPTABLE** (inadequate number of pregnant females.) The initial review noted that the study might be upgraded with the submission of positive control data and the missing pages, 13 - 23. These have been submitted as Record # 50456, Document 304-050. The positive control data on TEM is in Record # 50460, Document 304-050. The number of animals was noted in the review but not stressed. Re-review finds that the study remains unacceptable. Schreider, 8/12/86, and Gee, 4/23/87.

EPA one-liner: Gavage levels tested - 0, 0.5, and 2.0 gm/kg/day for five days. Negative. Core grade: Supplementary/adequate.

021/041 995146 "A Dominant Lethal Study with Compound 67019 (Oryzalin) in the Rat", (11/1979, Lilly Research, Study R-149). Dominant Lethal, Rat, Wistar-derived; Oryzalin, 99.0%; No dominant lethal mutagenic effect up to 5 g/kg; 10 males per group, mated 1:1 with females for 8 weekly periods. **UNACCEPTABLE**

(no positive control, only 10 females/mating period/group). Apostolou, 6/12/85 and Gee, 4/23/87.

EPA one-liner: Inadequate to generate valid data. Core grade: Inadequate.

051 050460 Supplement to 042729. Control with TEM for dominant lethal effect, test date 7/83, Study R00383 of Lilly.

Summary: Considered together, the two dominant lethal studies, each with major deficiencies (primarily in the number of pregnant females per group), and with the submission of a study in which the positive control, TEM, was active; the collective data are sufficient to indicate that oryzalin does not cause a dominant lethal effect in rats. No further studies are required at this time. J. Gee, 4/87.

DNA DAMAGE

041 042730 "The Effect of Oryzalin (Lilly Compound 67019) on the Induction of DNA Repair Synthesis in Primary Cultures of Adult Rat Hepatocytes - Study 810217-337-UDS", (6/81, Lilly Research). DNA repair; Oryzalin, 96.5%; primary rat hepatocytes exposed 20 hours to 0, 0.5, 1.0, 5.0, 10.0, 50.0, 100.0, 500.0, or 1000.0 nmols/ml; 1 culture per concentration, 20 nuclei per concentration counted for net grains. There was no evidence of an increase in grain count with test article; positive controls (MNNG and 1-AAF) were active. **ACCEPTABLE study with no adverse effect. Gee, 8/12/86.

EPA one-liner #1: Negative (at up to and including 100 nanomoles per ml). Core grade: Acceptable.

EPA one-liner #2: Negative in cultures of adult rat hepatocytes. Core grade: Adequate.

304-050 050459 4 page summary of 041 042730, above.

NEUROTOXICITY

Not required at this time.